

Claims:

1. A nucleic acid having covalently bonded to at least one nucleotide of the nucleic acid, a chelating agent, the covalently bonded chelating agent having an affinity for a transition metal ion.
2. The nucleic acid of claim 1 wherein the nucleic acid comprises a plurality of covalently bonded chelating agents.
3. The nucleic acid of claim 1 wherein the nucleic acid is chelated to a transition metal ion.
4. The nucleic acid of claim 3 wherein the transition metal ion is selected from the group consisting of  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ , and  $\text{Co}^{2+}$ .
5. The nucleic acid of claim 4 wherein the transition metal ion is  $\text{Ni}^{2+}$ .
6. The nucleic acid of claim 1 wherein the nucleic acid is labeled with a radioactive moiety.
7. The nucleic acid of claim 6 wherein the radioactive moiety is selected from the group consisting of  $^{32}\text{P}$ ,  $^{33}\text{P}$ ,  $^{35}\text{S}$ , and  $^3\text{H}$ .
8. The nucleic acid of claim 6 wherein the radioactive moiety is  $^{32}\text{P}$  and the  $^{32}\text{P}$  moiety is a 5' label or a 3' label.
9. The nucleic acid of claim 1 wherein the nucleic acid is labeled with a fluorescent moiety.
10. The nucleic acid of claim 1 wherein the nucleic acid is labeled with a biotin moiety.
11. A method of generating a nucleic acid having covalently bonded to at least one nucleotide of the nucleic acid, a chelating agent, the covalently bonded chelating agent having an affinity for a transition metal ion, the method comprises the steps of:
  - a. determining which nucleotides in a nucleic acid will be covalently

- bonded to the chelating agent; and
- b. synthesizing the nucleic acid utilizing a nucleotide having covalently bonded thereto a chelating agent determined in step (a).
12. The method of claim 11 wherein the nucleic acid in step (b) is synthesized by an enzymatic reaction.
13. The method of claim 12 wherein the enzymatic reaction utilizes an enzyme selected from the group consisting of a DNA polymerase, a PCR polymerase, an RNA polymerase, a reverse transcriptase, and mutants, variants, and derivatives thereof.
14. The method of claim 13 wherein the enzyme is a DNA polymerase and the DNA polymerase is derived from a mesophilic organism.
15. The method of claim 14 wherein the DNA polymerase derived from a mesophilic organism is selected from the group consisting of *E. coli* DNA polymerase I (proficient or deficient in 3' → 5' exonuclease activity), T4 DNA polymerase, and mutants, variants, and derivatives thereof.
16. The method of claim 13 wherein the enzyme is a PCR polymerase and the PCR polymerase is a thermostable polymerase.
17. The method of claim 16 wherein the thermostable polymerase is selected from the group consisting of *Taq*, *Tne*, *Tma*, *Tth*, *Pfu*, VENT<sup>™</sup>, DEEPVENT<sup>™</sup>, Pfx<sup>™</sup>, and mutants, variants and derivatives thereof..
18. The method of claim 12 wherein the enzymatic reaction is PCR.
19. The method of claim 12 wherein the nucleic acid is synthesized utilizing a nucleotide having covalently bonded thereto a chelating agent.
20. The method of claim 11 wherein the nucleic acid in step (b) is synthesized by a chemical reaction.

21. The method of claim 20 wherein the chemical reaction uses phosphoroamidite chemistry.
22. The method of claim 20 wherein the chemical reaction utilizes an automated oligonucleotide synthesizer.
23. A method of generating a nucleic acid having covalently bonded to at least one nucleotide of the nucleic acid, a chelating agent, the covalently bonded chelating agent having an affinity for a transition metal ion, the method comprises the steps of:
  - a. providing the nucleic acid; and
  - b. bonding the chelating agent to the nucleic acid with a crosslinking agent.
24. A nucleotide-chelating agent conjugate comprising a nucleotide having covalently bonded thereto a chelating agent, the covalently bonded chelating agent having an affinity for a transition metal ion.
25. The nucleotide of claim 24 wherein the nucleotide is a deoxyribonucleotide.
26. The deoxyribonucleotide of claim 24 wherein the deoxyribonucleotide is selected from the group consisting of dCTP, dATP, dGTP, dTTP, dITP and derivatives and analogs thereof.
27. The deoxyribonucleotide of claim 26 wherein the deoxyribonucleotide is dCTP.
28. The nucleotide of claim 24 wherein the nucleotide is a ribonucleotide.
29. The ribonucleotide of claim 27 wherein the ribonucleotide is selected from the group consisting of CTP, ATP, GTP, UTP and derivatives and analogs thereof.
30. The nucleotide of claim 24 wherein the chelating agent is NTA.
31. The nucleotide of claim 30 wherein the NTA is  $\alpha$ -N,N-bis-carboxymethyl lysine.

32. The nucleotide of claim 24 wherein the transition metal ion is selected from the group consisting of  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ , and  $\text{Co}^{2+}$ .
33. The nucleotide of claim 32 wherein the transition metal ion is  $\text{Ni}^{2+}$ .
34. A method of synthesizing a nucleotide-chelating agent conjugate, the method comprises the step of covalently bonding a chelating agent to a nucleotide to form the nucleotide-chelating agent conjugate, the covalently bonded chelating agent having an affinity for a transition metal ion.
35. The method of claim 34 wherein the step of coupling is enzymatic coupling.
36. The method of claim 35 wherein the enzymatic coupling utilizes an enzyme selected from the group consisting of pyrophosphatase, terminal nucleotidyl transferase, recombinase, ligase, isomerase, and a ribozyme.
37. The method of claim 34 wherein the step of coupling is chemical coupling.
38. The method of claim 37 wherein the chelating agent is NTA.
39. The method of claim 38 wherein the NTA is  $\alpha$ -N,N-bis-carboxymethyl lysine.
40. A method of chelating a transition metal ion to a nucleic acid having covalently bonded to at least one nucleotide of the nucleic acid, a chelating agent, the covalently bonded chelating agent having an affinity for a transition metal ion, the method comprises the steps of:
- a. mixing an excess of a transition metal ion and the nucleic acid to form a mixture;
  - b. incubating the mixture for a time to form a transition metal-chelating agent-nucleic acid chelate; and
  - c. purifying the transition metal-chelating agent-nucleic acid chelate from the excess transition metal ion.

41. The method of claim 40 wherein step (c) is performed by precipitation using 2% lithium perchlorate.
42. A method for detecting a polyhistidine-containing recombinant protein wherein the method comprises the steps of
  - a. forming a conjugate of a transition metal-chelating agent-nucleic acid chelate with the polyhistidine-containing recombinant protein; and
  - b. detecting the conjugate.
43. The method of claim 42 wherein the polyhistidine recombinant protein to be detected is present in a gel.
44. The method of claim 43 wherein the step of forming the conjugate is performed prior to resolving the protein mixture on the gel.
45. The method of claim 42 wherein the gel is selected from the group consisting of a semi-denaturing gel and a native gel.
46. The method of claim 45 wherein the gel is a semi-denaturing gel and the semi-denaturing gel further comprises 7M urea.
47. The method of claim 42 wherein the recombinant protein to be detected has been transferred to a membrane.
48. The method of claim 42 wherein the chelating agent is NTA.
49. The method of claim 48 wherein the NTA is  $\alpha$ -N,N-bis-carboxymethyl lysine.
50. The method of claim 42 wherein the transition metal-chelating agent-nucleic acid further comprises a label.
51. The method of claim 50 wherein the label is a radioactive label.
52. The method of claim 50 wherein the label is a fluorescent label.
53. The method of claim 50 wherein the label is a biotin label.

54. The method of claim 42 wherein the step of detecting the conjugate comprises His-tag amplification.
55. A method for His-tag amplification of a transition metal-chelating agent-nucleic acid chelate, the method comprises the step of amplifying the nucleic acid portion of the chelate.
56. The method of claim 55 further comprising the step of detecting the amplified nucleic acid.
57. The method of claim 55 wherein the step of amplifying the nucleic acid portion of the chelate comprises PCR.
58. The method of claim 55 wherein the step of amplifying the nucleic acid portion of the chelate comprises real-time PCR.
59. A method for identifying a peptide ligand that binds a biomolecule, wherein the peptide ligand is identified from a peptide library, the method comprises the steps of:
- (a) immobilizing the biomolecule;
  - (b) contacting the biomolecule with a peptide library, wherein the peptide library comprises peptides having a polyhistidine sequence;
  - (c) forming a conjugate of a transition metal-chelating agent-nucleic acid chelate with the polyhistidine sequence of the library peptides; and
  - (d) detecting the chelate.
60. The method of claim 59 wherein the step of immobilizing the biomolecule comprises immobilizing the biomolecule to a surface.
61. The method of claim 60 wherein the surface comprises the surface of a well of a multi-well plate.

62. The method of claim 59 wherein the step of detecting comprises His-tag amplification.
63. The method of claim 62 wherein the His-tag amplification includes real-time PCR.
64. The method of claim 59 wherein the chelate further comprises a moiety selected from the group consisting of a radioactive moiety, a fluorescent moiety, and biotin.
65. A method for identifying a biomolecule that can bind to a peptide ligand, the method comprises the step of:
  - (a) providing a biomolecule mixture;
  - (b) resolving the biomolecule mixture;
  - (c) immobilizing the biomolecule mixture;
  - (d) contacting the biomolecule mixture with a peptide library, wherein the peptide library comprises peptides having a polyhistidine sequence;
  - (e) forming a conjugate of a transition metal-chelating agent-nucleic acid chelate with the polyhistidine of the peptides; and
  - (f) detecting the chelate.
66. The method of claim 65 wherein the step of detecting comprises His-tag amplification.
67. The method of claim 66 wherein the His-tag amplification includes real-time PCR.
68. The method of claim 65 wherein the peptide further comprises a moiety selected from the group consisting of a radioactive moiety, a fluorescent moiety, and biotin.
69. A method for identifying a biomolecule that can bind to a peptide ligand, the method comprises the steps of:
  - (a) providing a biomolecule mixture;

- (b) contacting the biomolecule with a peptide library, wherein the peptide library comprises peptides having a polyhistidine sequence;
- (c) resolving the biomolecule mixture;
- (d) immobilizing the biomolecule mixture;
- (e) forming a conjugate of a transition metal-chelating agent-nucleic acid chelate with the polyhistidine of the peptides; and
- (f) detecting the chelate.

- 70. The method of claim 69 wherein the step of detecting comprises His-tag amplification.
- 71. The method of claim 70 wherein the His-tag amplification includes real-time PCR.
- 72. The method of claim 69 wherein the peptide further comprises a moiety selected from the group consisting of a radioactive moiety, a fluorescent moiety, and biotin.